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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/525,867	03/15/2000	Henry Yue	PF-0678US	9574

7590 03/12/2002

Legal Dept
Incyte Pharmaceuticals Inc
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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	9

DATE MAILED: 03/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/525,867	Applicant(s) YUE ET AL.	
	Examiner Delia M. Ramirez	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/3/2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 23-30* is/are pending in the application.

4a) Of the above claim(s) *1,2,7,9,12-15,23,26,27 and 29* is/are withdrawn from consideration.

5)☒ Claim(s) *4,24 and 25* is/are allowed.

6)☒ Claim(s) *3,5,6,8,10,11,28 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-15 and 23-30 are pending.

It is noted that the examination of the instant application has been assigned to a different Examiner in Group Art Unit 1652.

Applicant's election with traverse of Group II, claims 3-6, 8, 10, 11, drawn to the polynucleotide of SEQ ID NO: 9 and the polynucleotide encoding the polypeptide of SEQ ID NO: 1, host cells, vectors, and a method to produce the polypeptide of SEQ ID NO: 2, amendment of claims 4 and 23, cancellation of claims 16-22, and addition of claims 24-30 in Paper No. 8, filed on 1/3/2002 is acknowledged.

Applicant's traverse is on the ground(s) that Group I and II can be examined together without undue burden on the Examiner and that Groups V and XI should be examined together with Groups I and II in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103 (b) which set forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Furthermore, Applicants traverse the restriction requirement by arguing that SEQ ID NO: 1-8 (polypeptides) and SEQ ID NO: 9-16 (polynucleotides) are elements of a Markush group and therefore should be examined according to Markush practice. Applicants argue that the instant application claims 8 sequences and therefore the guidelines set forth in M.P.E.P. § 803.04 should be applied.

While it is true that publications containing polynucleotide (Group II) information such as open reading frame sequences typically disclose the corresponding polypeptide (Group I), it is false to assume that the only source of information about a polypeptide is one in which

polynucleotide information is disclosed. Therefore, the Examiner must search not only for polynucleotide but also for polypeptide information. In regard to the rejoinder of Groups V and XI, drawn to methods of use of the polynucleotide, it should be noted that the elected Group already contains claims to a method of use for the polynucleotide of SEQ ID NO: 9 (claims 8 and 25) which are drawn to the production of the protein of SEQ ID NO: 1 using the polynucleotide of SEQ ID NO: 9 Therefore, one method of use has already been elected and is already being examined according to *In re Ochiai, In re Brouwer* and 35 USC § 103 (b).

According to applicant's specification, the polypeptides encoded by the polynucleotides of SEQ ID NO: 9-16 (page 2 of the specification) are mitochondrial proteins with different amino acid sequences (SEQ ID NO: 1-8) which do not share a core structure or structural elements. Furthermore, Table 2 of the specification indicates that the polypeptides encoded by the polynucleotides of SEQ ID NO: 9-16 belong to different species, have different functions and structures. As stated in M.P.E.P. § 803.04, "Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another". Therefore, for the reasons stated above, the polypeptides of SEQ ID NO: 1-8 and the polynucleotides of SEQ ID NO: 9-16 are patentably distinct inventions and are not considered elements of Markush-type groups.

In regard to the number of sequences that can be examined in a single application, the guidelines set forth in M.P.E.P. § 803.04 clearly indicate that ***up*** to (***not at least***) 10 independent and distinct nucleotide sequences can be examined in a single application. Therefore, the number of nucleotide sequences to be examined in one single application can vary from 1 to 10. However, searching more than one nucleotide sequence per application will place an undue

burden upon the Examiner and the Office since the search of sequences is not co-extensive and the length of the search is sequence size-dependent.

The restriction requirement is deemed proper and therefore is made FINAL.

Claims 1-2, 7, 9, 12-15, 23, 26, 27, 29 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

1. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

If applicant desires priority under 35 U.S.C. 119 based upon a previously filed provisional application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The following format is suggested: "This application claims benefit of Provisional Application (#) under 35 USC 119(e)".

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "Isolated nucleic acid molecule encoding a human NADH-ubiquinone oxidoreductase".

Claim Objections

3. Claims 3, 8, 24, 28 are objected to under 37 CFR 1.75(c) as being in improper form because these claims depend on non-elected claims. For examination purposes, the limitations recited in the non-elected claims will be considered as being part of the elected claims when appropriate. Correction is required.

Double Patenting

4. It is noted that SEQ ID NO: 1 of the instant application is disclosed in Application No. 09/488,725 as SEQ ID NO: 2769 and 6341. Also SEQ ID NO: 670, as disclosed in Application No. 10/037,270, encodes the polypeptide of SEQ ID NO: 1 of the instant application. No determination as to whether or not double patenting issues would apply to the instant application has been made due to unavailability of Application No. 09/488,725 and 10/037,270 for examination at this time. Applicants should note that if interfering matter is found in Application No. 09/488,725 or 10/037,270 after they become available, double patenting will not be considered as new ground(s) of rejection.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 3, 8, 10 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 3 and 8 are indefinite in the recitation in claim 1 (from which claims 3 and 8 are dependent from) of "biologically active fragment" for the following reasons. The term "biologically active" has been defined in the specification (page 8, lines 27-28) as having structural, regulatory, or biochemical functions of a naturally occurring protein. This term, however, renders the claim vague and unclear because applicant's definition does not clarify which functions of the protein of SEQ ID NO: 1 are encompassed by the definition. The term "biologically active" can have many interpretations to one of skill in the art. For example, one interpretation in regard to a polypeptide is the ability to elicit antibodies. It is suggested that the term "biologically active" be replaced with a term that clearly defines applicant's intended biological function. In addition, the term "fragment" renders the claim vague and confusing because the size of a fragment has not been defined in the claim or in the specification, therefore one of skill in the art could not determine the metes and bounds of the claims. It is suggested that applicants clearly indicate the size of the fragment in the claim. For examination purposes, claims 3 and 8 will be interpreted as being directed to a polynucleotide encoding a fragment of any size of the amino acid sequence set forth in SEQ ID NO: 1 and to a method for producing said fragment.

8. Claim 10 (c) and (d) is indefinite in the recitation of "a polynucleotide sequence complementary to". Based upon Applicants' definition of "complementary" (page 8, lines 31-35, page 9, lines 1-4 of the instant specification) it is unclear whether the complementary strands are

partial or complete complements. It is suggested that Applicants clarify their meaning of the term complementary by replacing the term "a polynucleotide sequence complementary to" with, for example, "a polynucleotide sequence completely complementary to". For examination purposes, the language "polynucleotide sequence complementary to" will be interpreted as "polynucleotide sequence partially or completely complementary to".

9. Claim 30 is indefinite in the recitation of "first oligonucleotide or polynucleotide sequence specifically hybridizable with at least 30 contiguous nucleotides" for the following reasons. First, it is unclear what the term "first" refers to. Second, the term "specifically hybridizable" is unclear absent a statement indicating the conditions under which the hybridization/wash reaction takes place. Since nucleic acids which will hybridize under some hybridization conditions will not necessarily hybridize under different conditions, the array can comprise different nucleic acids depending on the hybridization conditions. For examination purposes, the Examiner will interpret the claim to be drawn to an array comprising a nucleic acid molecule of at least 30 contiguous nucleotides of the polynucleotide of claim 10.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide encoding the polypeptide of SEQ ID NO: 1, does not reasonably provide enablement for the polynucleotides encoding proteins with an amino acid sequence of at least 90% sequence identity to SEQ ID NO: 1, biologically active fragments of

SEQ ID NO: 1, or immunogenic fragments of SEQ ID NO: 1 . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8; USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

Claim 3 is so broad as to encompass any polynucleotide encoding a polypeptide with an amino acid sequence of at least 90% sequence identity to SEQ ID NO: 1, biologically active fragments of SEQ ID NO: 1, or immunogenic fragments of SEQ ID NO: 1. The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claim Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence to obtain the desired activity requires knowledge of and guidance with regard to which amino acids, if any, are tolerant of modification and which ones are conserved. Furthermore, detailed knowledge of how the polypeptide's structure relates to its function is required. As taught by Broun et al. (Science 282:1315-1317, 1998), as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase into a desaturase. In the instant case, the disclosure is limited to the polypeptide of SEQ ID NO: 1 and the corresponding polynucleotide as set forth in SEQ ID NO: 9.

The specification does not disclose any information about the critical structural elements within the amino acid sequence of SEQ ID NO: 1 that are required to maintain the desired function such as the catalytic domain, the binding domain, and the like. Therefore one of skill in the art would not know which segments within the amino acid sequence still retain the desired function or their size. Furthermore, the specification does not indicate which segments of the polypeptide are immunogenic, the minimum size required for an immunogenic fragment, or which immunogenic fragments can cause antibody cross-reactivity with other proteins. No examples of other polynucleotides encoding polypeptides with amino acid sequences having at least 90% sequence homology to SEQ ID NO: 1 or biologically active fragments of SEQ ID NO: 1 with the desired function are provided either.

The current state of the art indicates that small amino acid changes can drastically change the function of a polypeptide (see the teachings of Broun et al.). In addition, it is not routine in the art to randomly select fragments of a protein to determine if they still retain the desire function. Also, it is not routine in the art to determine the immunogenicity of a fragment by randomly selecting fragments of any size and inject them into animals to measure the level of antibody production. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to maintain the desired function, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to screen and isolate those molecules with the desired activity. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

12. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO: 9, does not reasonably provide enablement for any polynucleotide having at least 70% sequence homology to SEQ ID NO: 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

Claim 10 encompasses any polynucleotide having at least 70% sequence homology to SEQ ID NO: 9. The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claim. As indicated previously, the amino acid sequence of a polypeptide determines its structural and functional properties, therefore predictability of which changes can be tolerated in a polypeptide's amino acid sequence to obtain the desired activity requires knowledge of and guidance with regard to which amino acids, if any, are tolerant of modification and which ones are conserved. Furthermore, detailed knowledge of how the polypeptide's structure relates to its function is required. Broun et al. shows that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid

substitutions can transform a hydrolase into a desaturase. In the instant case, the disclosure is limited to the polypeptide of SEQ ID NO: 1 and the corresponding polynucleotide as set forth in SEQ ID NO: 9. The specification does not disclose any information about the critical structural elements within the nucleotide sequence of SEQ ID NO: 9 that are required to maintain the desired function in the corresponding polypeptide such as the catalytic domain, the binding domain, and the like. No examples of other polynucleotides having nucleotide sequences of at least 70% sequence identity to SEQ ID NO: 9 encoding a protein with the desired function are provided either.

The current state of the art indicates that small amino acid changes can drastically change the function of a polypeptide (see the teachings of Broun et al.). In addition, it is known in the art that sequence identity alone is insufficient to accurately predict function. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required to maintain the desired function, and the unpredictability of the prior art in regard to function based on homology, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to screen and isolate those molecules with the desired activity. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

13. Claims 11, 28 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO: 9, does not reasonably provide enablement for fragments of SEQ ID NO: 9 of at least 30 or 60 contiguous nucleotides and microarrays containing these fragments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

Claims 11, 28, and 30 are so broad as to encompass any fragment of 30 or 60 nucleotides of SEQ ID NO: 9 as well as microarrays containing these fragments. The scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. As indicated previously, the amino acid sequence of a polypeptide determines its structural and functional properties, therefore predictability of which segments of the polypeptide would retain its desired function requires some knowledge and guidance as to which amino acids are absolutely required for function. Detailed knowledge of how the polypeptide's structure relates to its function is required. In the instant case, the disclosure is limited to the polypeptide of SEQ ID NO: 1 and the corresponding polynucleotide as set forth in SEQ ID NO: 9. The specification does not disclose any information about the critical structural elements within the nucleotide sequence of

SEQ ID NO: 9 that are required to maintain the desired function in the corresponding polypeptide such as the catalytic domain, the binding domain, and the like. No information is provided on which polynucleotide fragments within SEQ ID NO: 9 are indicative of NADH-ubiquinone oxidoreductase function. No examples of other polynucleotides comprising at least 30 or 60 contiguous nucleotides of SEQ ID NO: 9 encoding a protein with the desired function are provided either.

The current state of the art indicates that small amino acid changes can drastically change the function of a polypeptide (see the teachings of Broun et al.). It is not routine in the art to randomly express fragments of a nucleic acid molecule and determine if the desired activity is retained. One of skill in the art would at least required some knowledge of which nucleotides within the given sequence encode known conserved regions of the protein in order to use a microarray containing a fragment of 30 or 60 nucleotides of SEQ ID NO: 9. Therefore, due to the lack of relevant examples, the amount of information provided, and the lack of knowledge about the critical structural elements required to maintain the desired function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to (1) screen and isolate those molecules encoding polypeptides with the desired activity or determining which domains are characteristic of proteins with similar function and (2) use these molecules in a microarray. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 3, 5, 6, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Hyslop et al. (Genomics 37:375-380, 1996). Hyslop et al. teaches cloning of the PSST subunit gene of human mitochondrial complex I (NADH-ubiquinone oxidoreductase, page 375, Abstract). Hyslop et al discloses the amino acid sequence (Figure 2, page 377) and the corresponding cDNA (Figure 1, page 376) of the PSST subunit. Hyslop et al. also discloses vectors and host cells comprising the DNA encoding the PSST subunit (page 376, column 2, Materials and Methods). The amino acid sequence of the PSST subunit of Hyslop et al. has a 99.1% sequence similarity to the polypeptide of SEQ ID NO: 1 with only one amino acid mismatch (see attached alignment). The cDNA sequence of the polypeptide of Hyslop et al. (648 nucleotides) when aligned to SEQ ID NO: 9 (824 nucleotides) presents a best local similarity of 99.5% (calculated as % best local similarity = number of identical residues (matches=645)*100/(length of alignment=648). All of the cDNA of Hyslop et al. except for 3 mismatches at positions 68, 644 and 647 (Figure 1, page 375) is comprised by SEQ ID NO: 9 of the instant application. It is noted that for visualization purposes, the attached DNA alignment uses the sequence of chromosome 19, which contains the genomic sequence of the PSST subunit (introns are shown as gaps). Introns were not used in the % similarity calculation and the mismatches between SEQ ID NO: 9 and the cDNA of Figure 1 are shown in the attached alignment in red.

Claim 3 is drawn in part to a polynucleotide encoding a polypeptide having 90% sequence identity to SEQ ID NO: 1, a biologically active fragment of SEQ ID NO: 1, or an immunogenic fragment of SEQ ID NO: 1. Claim 5 is drawn in part to a recombinant

polynucleotide comprising a promoter operably linked to the polynucleotide of claim 3, claim 6 is drawn to a host cell comprising the polynucleotide of claim 3, and claim 11 is partially drawn to a fragment of SEQ ID NO: 9 (or complement thereof) which is at least 60 nucleotides in length. Therefore, the PSST subunit and corresponding cDNA, vectors, and host cells of Hyslop et al. anticipate claims 3, 5, 6, and 11 as written.

15. Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Hyslop et al. (Genomics 37:375-380, 1996). As indicated above, Hyslop et al. teaches a cDNA molecule encoding a PSST subunit of 648 nucleotides which is comprised by SEQ ID NO: 9 of the instant application except for 3 mismatches at positions 68, 644, and 647 of the cDNA of Hyslop et al. The cDNA sequence of the polypeptide of Hyslop et al. (648 nucleotides) when aligned to SEQ ID NO: 9 (824 nucleotides) has a 99.5% sequence homology with the entire coding sequence (see calculation above). If nucleotides 1-78 and 726-824 of SEQ ID NO: 9, which are not part of the coding sequence, are considered mismatches (they are not present in the cDNA of Hyslop et al. as disclosed in Figure 1), this cDNA molecule has 72 % sequence identity to SEQ ID NO: 9 (% similarity = [(matches=645) – (mismatches=176+3)]x100/(query sequence length=648). Claim 10 is directed to polynucleotides of at least 70% sequence homology to SEQ ID NO: 9, therefore the cDNA of Hyslop et al. anticipates the instant claims as written.

16. Claims 3, 5, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Arizmendi et al. (FEBS Lett. 301:237-242, 1992; Swiss Prot accession number P42026, November 1, 1995). Arizmendi et al. teaches a bovine NADH-ubiquinone oxidoreductase subunit with 86.4% amino

acid sequence homology to SEQ ID NO: 1 and several fragments with 100% sequence homology to SEQ ID NO: 1, including a fragment of 100 amino acids (see alignment). Arizmendi et al. also teaches vectors and host cells comprising the cDNAs encoding the NADH-ubiquinone oxidoreductase subunit (page 238, column 2, first paragraph; Figure 2, page 239, caption).

Claim 3 is drawn in part to a polynucleotide encoding a biologically active fragment of SEQ ID NO: 1 and an immunogenic fragment of SEQ ID NO: 1. Claim 5 is drawn to a recombinant polynucleotide comprising a promoter operably linked to the polynucleotide of claim 3 and claim 6 is drawn to a host cell comprising the polynucleotide of claim 3. The fragment of 100 amino acids can contain an immunogenic epitope and also be biologically active. Therefore, the PSST subunit and corresponding cDNA, vectors, and host cells of Arizmendi et al. anticipate claims 3, 5, and 6 as written.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hyslop et al. (Genomics 37:375-380, 1996). Hyslop et al. teaches cloning of the PSST subunit gene of human mitochondrial complex I (NADH-ubiquinone oxidoreductase, page 375, Abstract). Hyslop et al discloses the amino acid sequence (Figure 2, page 377) and the corresponding cDNA (Figure 1, page 376) of the PSST subunit. Hyslop et al. also discloses vectors and host cells comprising the DNA encoding the PSST subunit (page 376, column 2, Materials and Methods). The amino acid sequence of the PSST subunit of Hyslop et al. has a 99.1% sequence similarity to the polypeptide of SEQ ID NO: 1 with only one amino acid mismatch. Hyslop et al. does not teach a method to produce the PSST subunit using the host cell transformed with a vector comprising the cDNA encoding the PSST and recovering said protein.

Claim 8 is partially directed to a method of producing a polypeptide having an amino acid sequence identity of at least 90% to SEQ ID NO: 1, a biologically active fragment of SEQ ID NO: 1, or an immunogenic fragment of SEQ ID NO: 1 comprising culturing a transformed host and recovering the polypeptide.

It would have being obvious to one of ordinary skill in the art at the time the invention was made to culture the host cells transformed with the vector comprising the cDNA encoding the protein of Hyslop et al. to produce the protein and recover it from the medium. One of ordinary skill in the art would have been motivated to express the protein with the transformed host cells of Hyslop et al. and recover the protein to obtain enough material for further

characterization studies. One of ordinary skill in the art has a reasonable expectation of success at expressing the protein of Hyslop et al. with the transformed host cells of Hyslop et al. because it is routine in the art to transform cells with vectors comprising the DNA encoding the protein of choice, culture the host cells to express the protein, and recover the protein from the culture medium. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

20. Claims 28 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hyslop et al. (Genomics 37:375-380, 1996). The teachings of Hyslop et al. have been discussed above. Hyslop et al. does not teach microarrays containing the cDNA disclosed by Hyslop et al.

Claim 28 is partially directed to a microarray containing a nucleic acid molecule comprising at least 60 nucleotides of SEQ ID NO: 9 (or complement thereof, or the RNA equivalent). Claim 30 is partially directed to a microarray containing a nucleic acid molecule comprising at least 30 nucleotides of SEQ ID NO: 9 (or complement thereof, or the RNA equivalent).

It would have being obvious to one of ordinary skill in the art at the time the invention was made to make a microarray wherein at least one the polynucleotides is a fragment of the cDNA (or complement thereof, or the RNA equivalent) of Hyslop et al. One of ordinary skill in the art would have been motivated to use a fragment of the cDNA (or complement thereof, or the RNA equivalent) of Hyslop et al. in a microarray because microarrays are used for high-throughput screening of nucleic acid molecules for gene expression analysis, gene discovery, etc., therefore the cDNA of Hyslop et al. (or fragment thereof) could be used to detect other

homologous nucleic acid molecules which encode proteins of similar function. One of ordinary skill in the art has a reasonable expectation of success at making the microarray with the cDNA of Hyslop et al. (or complement thereof, or fragment thereof) because it is routine in the art to deliver and immobilized nucleic acid molecules onto small coated surfaces to create microarrays. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

21. Claims 4, 24 and 25 appear to be allowable over the prior art of record. Claim 4 is directed to an isolated polynucleotide comprising the polynucleotide sequence as set forth in SEQ ID NO: 9. Claim 24 is directed to an isolated polynucleotide encoding a polypeptide comprising SEQ ID NO: 1. Claim 25 is directed to a method of producing the polypeptide of SEQ ID NO: 1. The prior art of record does not teach a polypeptide with 100% sequence identity to the polypeptide of SEQ ID NO: 1 or a polynucleotide with 100% sequence identity to the polynucleotide of SEQ ID NO: 9, therefore an isolated polynucleotide encoding a polypeptide comprising SEQ ID NO: 1, a method of producing the polypeptide of SEQ ID NO: 1, or a polynucleotide comprising the polynucleotide sequence of SEQ ID NO: 9 do not appear to be anticipated by the prior art of record.

22. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

23. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
March 7, 2002

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